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(81) Designated States (*unless otherwise indicated, for every
kind of national protection available*): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
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GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
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ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: LIPOSOMAL FORMULATIONS COMPRISING A COMBINATION OF TWO OR MORE ACTIVE AGENTS

(57) Abstract: The present invention provides a composition comprising a physiologically acceptable carrier and two or more agents encapsulated in a liposome, wherein the combination of the two or more agents possess the following properties: (1) cytotoxicity to tumor cells, (2) nutritional properties, (3) use in application to nails, hair, skin or lips or (4) activity against parasites and insects. The invention also provides a method of making such a composition. The invention further provides the use of said composition for a manufacture of a medicament for treating cancer when the combination of the two or more agents is cytotoxic to tumor cells.

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US2004/016413

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/127 A61P35/00 A61P17/00 A61P31/00 A61P33/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>US 4 774 085 A (FIDLER ISAIAH J) 27 September 1988 (1988-09-27)</p> <p>claims 1-8 column 2, line 35 - column 6, line 52 ----- -/--</p>	<p>1,2, 14-16, 22-28, 30,42, 43, 56-62, 85,96</p>

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/016413

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 952 408 A (RAHMAN AQUILUR) 28 August 1990 (1990-08-28) claims 1-11 column 2, line 30 - column 4, line 29 -----	1,2, 10-16, 22-29, 42-50, 56-62, 80, 85-87,95
X	WO 01/95946 A (TRANSGENE SA) 20 December 2001 (2001-12-20) claims 1-26 page 10, line 20 - page 38, line 32 -----	1,2, 11-16, 22-28, 30-32, 38,39, 42-50, 56-62, 81,82, 85-87, 93,96,97
X	WO 01/34130 A (BOULIKAS TENI) 17 May 2001 (2001-05-17) claims 1-28 page 9, line 1 - page 28, line 5 -----	1,2, 14-16, 22-37, 42,43, 48-50, 56-65, 82, 85-87, 95,96
X	WO 01/34116 A (GEROLYMATOS P N SA) 17 May 2001 (2001-05-17) claims 1-14 page 9, line 5 - page 16, line 30 example 4 ----- -/--	1,2, 14-16, 20, 22-28, 42,43, 48-50, 54,56-62

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/016413

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 98/43095 A (UNIV GEORGETOWN) 1 October 1998 (1998-10-01)</p> <p>claims 1-16 page 3, line 20 - page 19, line 33 -----</p>	<p>1,2, 14-16, 18, 22-36, 38,42, 43, 48-50, 52, 56-64, 85-87, 91-98</p>
X	<p>WO 93/18751 A (UNIV GEORGETOWN) 30 September 1993 (1993-09-30)</p> <p>claims 1-18 page 4, line 9 - page 6, line 11 -----</p>	<p>1,2, 10-20, 22-30, 35-37, 42-69, 71-73, 75-80, 85-91, 95,96</p>
X	<p>DE 101 31 796 A (BEIERSDORF AG) 16 January 2003 (2003-01-16)</p> <p>claims 1-8 paragraph '0022! - paragraph '0110! -----</p>	<p>1,5,6,8, 10-16, 22-28</p>
X	<p>DE 39 36 328 A (SCHERING AG) 2 May 1991 (1991-05-02)</p> <p>claims 1-5 examples 3,4,7 column 1, line 10 - column 2, line 66 -----</p>	<p>1,5,6,8, 10-16, 22-28</p>
A	<p>US 6 090 955 A (BRANDL MARTIN ET AL) 18 July 2000 (2000-07-18) claims 1-15 column 2, line 19 - column 2, line 39 column 4, line 8 - column 4, line 19 -----</p>	<p>1-98</p>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/016413

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 42-85 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 4774085	A	27-09-1988	CA 1295239 C	04-02-1992
US 4952408	A	28-08-1990	AT 103172 T	15-04-1994
			AU 625308 B2	09-07-1992
			AU 3742489 A	12-12-1989
			CA 1339077 C	29-07-1997
			DE 68914154 D1	28-04-1994
			DE 68914154 T2	20-10-1994
			DK 279890 A	23-11-1990
			EP 0416014 A1	13-03-1991
			IE 64513 B1	09-08-1995
			JP 3504381 T	26-09-1991
			WO 8911292 A1	30-11-1989
WO 0195946	A	20-12-2001	AU 6938501 A	24-12-2001
			CA 2412842 A1	20-12-2001
			EP 1289568 A2	12-03-2003
			WO 0195946 A2	20-12-2001
			JP 2004506617 T	04-03-2004
			US 2002025941 A1	28-02-2002
WO 0134130	A	17-05-2001	US 6511676 B1	28-01-2003
			AU 777151 B2	07-10-2004
			AU 1104801 A	06-06-2001
			CA 2358948 A1	17-05-2001
			CN 1343118 T	03-04-2002
			EP 1156789 A1	28-11-2001
			GR 2000100384 A	31-07-2001
			JP 2003513911 T	15-04-2003
			WO 0134130 A1	17-05-2001
			US 2003185879 A1	02-10-2003
WO 0134116	A	17-05-2001	GR 1003509 B1	04-01-2001
			US 6652877 B1	25-11-2003
			AU 773462 B2	27-05-2004
			AU 1166201 A	06-06-2001
			CA 2390553 A1	17-05-2001
			EP 1253909 A2	06-11-2002
			WO 0134116 A2	17-05-2001
			JP 2003513902 T	15-04-2003
WO 9843095	A	01-10-1998	US 6126965 A	03-10-2000
			AU 749927 B2	04-07-2002
			AU 8938098 A	20-10-1998
			CA 2288613 A1	01-10-1998
			EP 0983513 A1	08-03-2000
			US 2003215489 A1	20-11-2003
			WO 9843095 A1	01-10-1998
			US 2003229040 A1	11-12-2003
			US 6333314 B1	25-12-2001
			US 6559129 B1	06-05-2003
			US 2002160038 A1	31-10-2002
WO 9318751	A	30-09-1993	AT 194767 T	15-08-2000
			AU 3922193 A	21-10-1993
			CA 2132711 A1	30-09-1993
			DE 69329073 D1	24-08-2000
			DE 69329073 T2	18-01-2001

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/016413

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9318751	A	DK 706373 T3	18-09-2000
		EP 0706373 A1	17-04-1996
		ES 2148223 T3	16-10-2000
		GR 3034024 T3	30-11-2000
		PT 706373 T	30-11-2000
		WO 9318751 A1	30-09-1993
		US 5424073 A	13-06-1995
		US 5648090 A	15-07-1997
DE 10131796	A	16-01-2003	DE 10131796 A1
DE 3936328	A	02-05-1991	DE 3936328 A1
		AT 103804 T	15-04-1994
		AU 6553790 A	02-05-1991
		CA 2028629 A1	28-04-1991
		WO 9106284 A1	16-05-1991
		DE 59005281 D1	11-05-1994
		DK 451237 T3	18-07-1994
		EP 0451237 A1	16-10-1991
		GR 90100772 A	20-03-1992
		HU 57590 A2	30-12-1991
		IE 903859 A1	08-05-1991
		JP 3011762 B2	21-02-2000
		JP 4503676 T	02-07-1992
		NO 912435 A	21-06-1991
		PT 95697 A , B	13-09-1991
		US 5723146 A	03-03-1998
US 6090955	A	18-07-2000	DE 4430593 A1
		AT 192924 T	15-06-2000
		DE 4447770 C2	19-12-2002
		WO 9605821 A1	29-02-1996
		DE 59508360 D1	21-06-2000
		DK 776202 T3	13-11-2000
		EP 0776202 A1	04-06-1997
		GR 3034162 T3	30-11-2000